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THE INFLUENCE OF CALCIUM ON MYOCARDIAL DEPRESSION CAUSED BY PENTOTHAL (AS STUDIED BY HIGH FREQUENCY CARDIOMYOGRAPHY)*)

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A FALL in blood pressure occasionally occurs during intravenous anaesthesia with various barbiturate preparations (Wezler and Thauer 1942, Adams 1944, Duesberg and Schroeder 1944, Buhr 1951). Some authors have attributed this fall in pressure to a direct action of barbiturates on the myocardium (Roth 1935, Johnson 1936, 1938, Gruber 1937). Others have disagreed and maintain that decreases in blood pressure are due to vasomotor reactions occurring in the peripheral vascular bed (Jacobi and Roemer 1911, Haynal and Held 1950, Nikolajev 1948, Harris 1951, Švec 1953). Convulsive analeptics, such as picrotoxin, metrazol, etc., have no effect in these cases, however (Adams 1944, Locket and Angus 1952, Shoewald 1940, Stephenson 1953).

On the whole, relatively little attention has been devoted to the question of the hypotensive effects of intravenous barbiturate anaesthesia, since blood pressure levels fall by a maximum of 20 mm. Hg in patients with normal tension. Any larger fall in blood pressure is caused rather by toxic doses. Adams has shown that even with moderate levels of pentothal anaesthesia, the blood pressure in hypertensive patients often falls by about 60 mm. Hg. With such marked lowering of pressure a sudden decrease in coronary blood flow threatens those patients who already suffer from latent or frank ischaemic cardiac disease. The risk is also increased in patients in whom this effect of pentothal anaesthesia is superimposed upon an already lowered blood pressure, as, for example, in shock. An unusually high mortality rate was found in shocked patients following the Pearl Harbour air raid, when conditions necessitated the use of i. v. barbiturate anaesthesia (Adams 1944). Harris (1951) mentions the observation of McMartin that patients with dysentery are abnormally sensitive to ordinary doses of sodium pentothal.

*) Abbreviated version presented at the IIIrd Congress of Czechoslovak Physiologists, Pharmacologists and Biochemists, Prague 1954.

The decrease in blood pressure during i. v. barbiturate anaesthesia is, therefore, not without importance, and in certain cases it is very much in the patient's interest to bring about a return of blood pressure to the original level as quickly as possible.

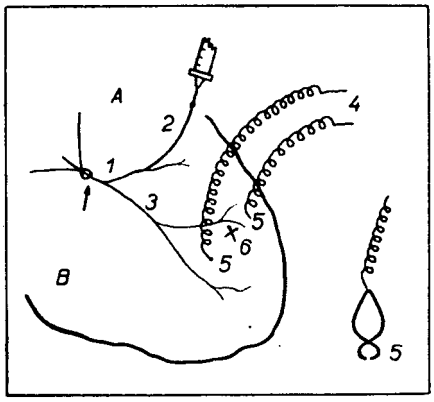


Fig. 1. Topographical sketch of the placing of high frequency cardiomyography electrodes (5), catheters (2), descending branch of left coronary artery (3), side branch (1), left ventricle (A), right ventricle (B); arrow marks the site of occlusion.

In the studies to be reported the factors causing a decrease in the blood pressure during intravenous anaesthesia with sodium pentothal (ethyl, 1-methyl. butyl, sodium thiobarbiturate) were more closely analysed and an attempt was made to influence this decrease therapeutically. The effect of this therapeutic intervention on the duration and depth of anaesthesia was also investigated.

METHODS

Experiments were carried out on a total of 15 dogs (weight 18—25 kg.), 12 dogs under initial light pentothal anaesthesia (30 mg./kg. body weight), and 3 under initial chloral anaesthesia (100 mg./kg). Mean arterial blood pressure was recorded from the femoral artery, using a mercury manometer.

In eight experiments, simultaneous measurements of aortic blood pressure were taken with a condensor manometer (Hansen 1949) as well as the type designed by Vokoun (1953). In addition, myocardial contraction was registered by means of high frequency cardiography (Froněk and Píša, 1954), and the ECG was recorded from an epicardial wick electrode moistened with physiological saline.

In a series of six experiments, 25—50 mg. of sodium pentothal were introduced, over a 20-second period, directly into a previously prepared side branch of the left descending coronary artery, according to the method of Tennant (1935). This method was modified so as to introduce a fine nylon

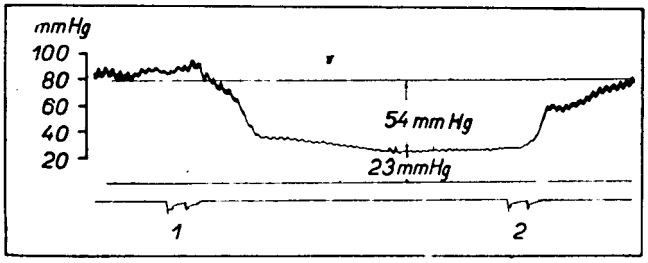


Fig. 2. The course of the blood pressure following intravenous administration of sodium pentothal (P) and $CaCl_2$ (CA). The blood pressure falls from 54 mm. Hg to 23 mm. Hg.

catheter into the artery through which test material could be injected. The advantage of this method lies in the fact that the blood stream carries the test solution injected into the left descending coronary artery, into an intact area (where myography electrodes and ECG are placed), and does not involve damaging the area supplied by the descending branch itself (fig. 1.).

In a further series of experiments we investigated the effect of administering 10% $CaCl_2$ intravenously on the duration and depth of pentothal anaesthesia. The studies were carried out in rabbits weighing 2.5—3.5 kg. All animals were injected with sodium pentothal, 45 mg./kg. body-weight, at the rate of 25 mg. pentothal per minute. The duration and depth of anaesthesia were estimated as described by Magnus and Girundt (1922, 1926 and 1932), at three minute intervals. Ten rabbits, forming the control group, received pentothal only. 24 animals were given in addition 10% $CaCl_2$ in doses of 90 mg./kg. immediately after the completion of the pentothal injection. Duration and depth of narcosis were then estimated in the same manner in both groups.

METHOD OF HIGH FREQUENCY CARDIOMYOGRAPHY

In essence this method registers changes in high frequency current, as measured across two electrodes, originating in changes of the impedance of heart muscle (fig. 1, e). The electrodes are fixed to the heart surface in experimental animals. One can use a high frequency bridge or a voltage divider

circuit, supplied by a generator at 300 Kc/second. Rhythmic changes in resistance occurring between the electrodes imbalance one side of the bridge, or the potentiometer. An electronic voltmeter with pre-amplifier, coupled in the usual way, can be used as the recorder system. We have worked with an

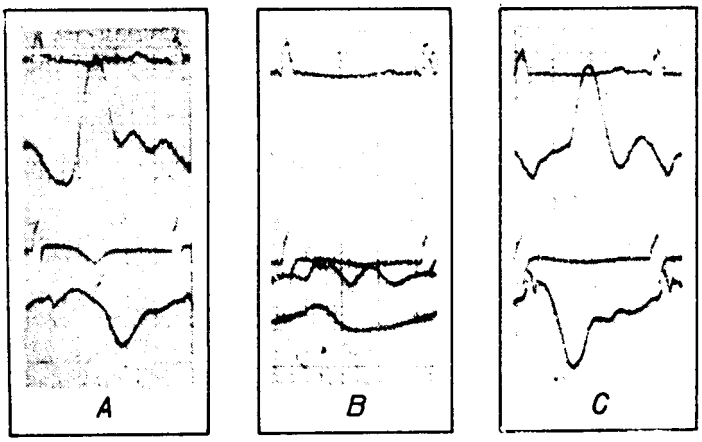


Fig. 3. Recording of changes in blood pressure and cardiac muscle contraction following I. V. administration of 500 mg. sodium pentothal (b) and 5 ml. $CaCl_2$ (c). Control record before administration (a). Order of curves: 1. ECG (standard lead II). 2. Aortic blood pressure. 3. Epicardial ECG. 4. High frequency cardiomyogram.

instrument designed by Vokoun (1952) for impedance plethysmography. Small spring clamps weighing 0.1 g. were used as electrodes. In systole, when the electrodes approach each other, the resistance between them decreases (which appears in our records as a downward movement of the curve), and then, as the electrodes diverge in diastole, the resistance across them increases. By detailed analysis of curves thus obtained and simultaneous recordings of epicardial ECG and aortic and left ventricular blood pressure, we have found it possible to distinguish, in these myographic curves, the separate phases of systole and diastole, as described by Wiggers (1949).

It has been possible to show, following a detailed analysis of this method, that alteration in resistance between the electrodes and, therefore, the shape of the curves is primarily the result of changes in the distance separating the electrodes. The possibility of phasic changes, caused by the coronary flow, has been excluded by experiments in which myocardiographic curves were recorded continuously before and after occlusion of a coronary artery. These showed that the curves do not change immediately following occlusion, when the flow

in the coronary bed ceases. Changes only appear, on an average, some 10 systoles after occlusion, when the actual nature of contraction in the ischaemic portion of myocardium has altered (Píša and Froněk 1954). Changes in the thickness of the heart muscle, which could account for the alteration in resist-

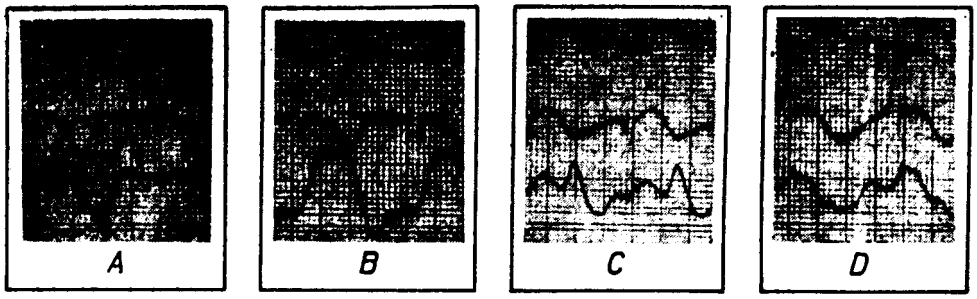


Fig. 4. Changes in myocardial contraction following intracoronary injection of first, 50 mg. sodium pentothal and; subsequently, 1 ml. isotonic $CaCl_2$. Order of curves from above downward: Aortic blood pressure, epicardial ECG, high frequency cardiomyography. A - control record preceding injection, B - changes in myographic curve 10 seconds after beginning pentothal injection (total time for injection was 20 seconds). 20 seconds after completion of pentothal injection, intracoronary injection of $CaCl_2$ was begun, also taking 20 seconds for completion. C - Recording of changes in myographic curve 7 seconds after beginning $CaCl_2$ injection. D - Record taken 20 seconds after completion of $CaCl_2$ injection.

ance, varying in the same direction. One finds that as the heart wall becomes thinner, the electrodes diverge and the resistance rises, and conversely.

Variation in ionic equilibrium or pH could affect the specific tissue resistance and thus the myographic findings. Such pH and ionic equilibrium changes, however, are not phasic but relatively slow (Frunder 1951). They could not, therefore, be expected to influence a myographic record obtained using an R—C coupled amplifier. In order to exclude, however, any possible influence of slow changes on the genesis of the high frequency myograph, we recorded myographs following occlusion of the descending branch of the left coronary artery both with a D—C coupled amplifier, which would pick up even the slowest changes, and with a condensor coupled (R—C) amplifier ordinarily used. No fundamental differences were found in the myographic curves recorded with the two circuits. In other words, slow tissue changes, pH or ionic, do not affect myographic records to any significant extent.

This method of high frequency cardiomyography is suitable for studying physiological and pathophysiological problems associated with myocardial contraction.

RESULTS

I. EFFECT OF INTRAVENOUS ADMINISTRATION OF PENTOTHAL

Thirteen dogs were given pentothal intravenously in doses which caused lowering of the blood pressure to levels of about 30 mm. Hg. Fig. 2 shows the blood pressure course following i. v. injection of 500 mg. of pentothal. Comparable falls in pressure occurred in all 13 experiments (tab. I). In these experiments in which the thoracic cavity was open, the pericardial sac sutured open and the heart under direct vision, we were able to detect weakening of cardiac contraction associated with the decrease in blood pressure, in most cases. The changes in aortic pressure and cardiac contraction are shown in fig. 3. In this particular record both the blood pressure fall and weakening of contraction were very marked (fig. 3, b).

One can conclude from these experiments that a weakening of myocardial contractile strength plays an important role in the hypotension occurring under these experimental conditions.

II. EFFECT OF INTRACORONARY ADMINISTRATION OF PENTOTHAL

The direct action of pentothal on the myocardium was further confirmed in another series of experiments, in which different concentrations of pentothal (25—50 mg. kg.) were injected directly into a coronary artery.

One can postulate that, if sodium pentothal caused reduction in contractile strength of that part of the myocardial muscle into which it was injected, the resulting myographic curve would alter, not only in consequence of this weakening of affected musculature, but that changes recorded from the damaged muscle would be exaggerated by increasing intraventricular pressure during systole of the intact muscle. That is to say, that the damaged muscle would be overstretched during systole and that, instead of contraction, one should find ballooning of the muscle. The myographic picture would thus be entirely reversed since the electrodes during systole would be diverging rather than converging. This would produce a picture similar to that following occlusion of a coronary artery (fig. 5). In fig. 4 we see that, following intracoronary administration of 50 mg. sodium pentothal in 20 secs., such changes in contraction of the affected muscle do in fact occur, and the myographic curve is completely inverted (fig. 4, b). In other words, the damaged myocardial muscle undergoes aneurysmal dilatation during systole.

These findings indicate that sodium pentothal acts directly on the myocardium, causing reduction of contractile strength.

We have sought some means of reversing this depressant action of pentothal on the myocardium. It is known that calcium stimulates myocardial

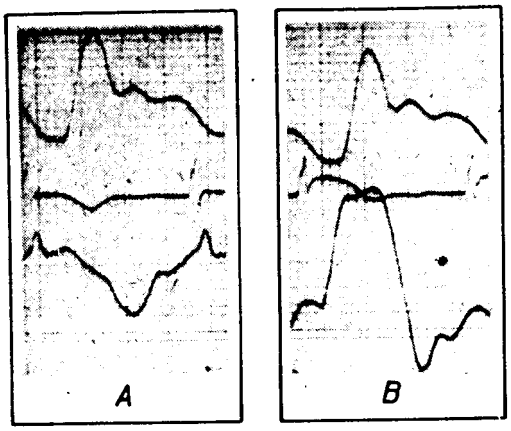


Fig. 5. High frequency cardiomyogram taken before and after occlusion of the descending branch of the left coronary artery. Order of curves: as in Figure 4.

contraction (Beck and Mautz 1937, Dale 1952, Danielopolu 1922, Gross 1953, Kay and Blalock 1951, Kunzová 1941, Rothlin and Cerletti 1952). We therefore tried to abolish the effect of pentothal on the myocardium with calcium. Fig. 2 shows rapid restoration of the lowered blood pressure following the intravenous injection of 5 ml. of 10% $CaCl_2$. In 12 out of 13 trials, the blood pressure returned almost to original levels after the i. v. administration of calcium. In the 13th, which was unsuccessful, the pentothal intoxication had been repeated within a short period of time. In fig. 3c are shown not only blood pressure changes following intravenous $CaCl_2$, but also striking alteration in myographic curves reflecting changes in the strength of myocardial contraction.

The results of intracoronary injection of isotonic $CaCl_2$, after pentothal depression as was already established represent further evidence that the hypotensive action of pentothal is a cardiac one. Fig. 4 illustrates a typical experiment in which the picture of myocardial dilatation was evoked by intracoronary injection of pentothal. Twenty seconds after the completion of the pentothal

injection, 1 ml. isotonic $CaCl_2$ was given by the same route. The rapid recovery of cardiac muscle function is evident in the myographic curves shown in fig. 1, C and D. In contrast, in control experiments, changes caused by intracoronary pentothal lasted more than 40 seconds.

III. EFFECT OF CALCIUM ADMINISTRATION ON THE DURATION AND DEPTH OF ANAESTHESIA

In order to ascertain whether intravenous calcium had any influence on the duration and depth of pentothal anaesthesia, tests were carried out in 34 rabbits. In the ten rabbits, forming the control group, which received only pentothal, anaesthesia lasted an average of 41.9 minutes. (tab. II). In a second group of 24 animals, $CaCl_2$ was given immediately after the pentothal, and in this group the average duration of anaesthesia was 35.5 minutes. The difference between the groups was not statistically significant ($P = 0.5$). The effect of calcium on the depth of pentothal anaesthesia was also investigated. Different stages of anaesthesia were determined as described by Magnus and Girundt. In tab. II are summarized the average lengths of time after the administration of pentothal when the signs of the various stages of anaesthesia appeared in the animals. Differences in the course of narcosis between the control group and the group receiving $CaCl_2$ were not significant.

DISCUSSION

One can conclude from the experiments described above that an important, if not the chief, cause of hypotension during intravenous pentothal anaesthesia is the direct depressant action of this barbiturate on the myocardium. This conclusion is in agreement with recent experimental work, explaining anaesthetic collapse by a fall in cardiac output with considerable increase in peripheral vascular resistance (Buhr 1951, Duesberg and Schroeder 1944, Wezler and Thauer 1942). We fully realise that the doses of pentothal used in our experiments are toxic. Due to the unequivocal efficacy of calcium in restoring blood pressure levels in clinical trials (see below), it can be postulated, however, that hypotension following ordinary doses of pentothal is brought about by the direct action of pentothal on the myocardium. It would be very difficult to explain this therapeutic efficiency of calcium, which itself acts as a vasodilator (Rothlin and Cerletti 1952), if hypotension during pentothal anaesthesia were a result of vasodilatation occuring in the face of an unchanged cardiac output.

Table I.

Exp. No.	Date	Anaesthesia	Dose of pentothal	Dose of $CaCl_2$	Blood pressure (mm. Hg.)			Remarks
					initial	following pentothal	following $CaCl_2$	
1	4. 3. 54	Pentothal 1 g.	0.25 g.	1 g.	110	0	90	
2	17. 3. 54	Pentothal 0.9 g.	0.1 g.	1 g.	80	18	60	
3	31. 3. 54	Pentothal 0.9 g.	0.5 g.	0.9 g.	110	20	105	
4	5. 4. 54	Pentothal 2 g.	2×0.5 g.	1 g.	130	80	120	
5	8. 4. 54	Pentothal 1 g. + 100 mg chloralose	0.2 g.	0.5 g.	77	23	80	
6	8. 4. 54	Pentothal 1 g. + 100 mg. chloralose	0.6 g.	1 g.	72	0	unsuccessful (same dog as 5, repeat experiment)	
7	21. 4. 54	Pentothal 1 g.	0.4 g.+ 0.3 g.	1 g.	134	22	125	
8	21. 4. 54	Pentothal 1 g.	0.3 g.	1 g.	95	15	80 later 95	
9	26. 4. 54	Pentothal 0.15 g. + chloralose 1.2 g.	0.6 g.		84	18	106	
10	28. 4. 54	Pentothal 1 g.	0.5 g.	1 g.	98	40	100	
11	5. 5. 54	Pentothal 1 g.	0.4 g.	1 g.	115	45	95	
12	8. 6. 54	Chloralose 2.4 g.	0.5 g.	1 g.	93	36	93	
13	9. 6. 54	Chloralose 2.02 g.	0.3 g.	0.5 g.	105	55	88	

Table II.

	No. of animals	Duration of anaesthesia (minutes)	Depth of anaesthesia (time in minutes following completion of pentothal injection when different stages appeared)			
			IV	III	II	I
Control Group pentothal only	10	41.9	8.8	15.4	25.0	31.0
$CaCl_2$ given after pentothal	24	35.5	11.8	18.3	24.6	29.6

It is difficult to determine whether the therapeutic effect of calcium in our experiments can be ascribed to a tonic effect of calcium on the myocardium or to pentothal detoxication by calcium in the body. One would expect that if detoxication of pentothal were involved, calcium would influence narcosis also, either by shortening the duration of pentothal anaesthesia or affecting its depth. This did not occur in our experiments. We may therefore assume some interference by calcium with myocardial metabolism.

Kunzová (1941) found that it was possible to abolish the depressant action of some barbiturates on the frog's heart by alkalizing the surrounding bath with $NaHCO_3$. In these experiments, no alkalization was involved, since the solution of $CaCl_2$ employed was neutral, and the chloride ion in the body causes extracellular acidosis. Furthermore, Kunzová was unable to reverse the myocardial depression caused by evipan by means of $NaHCO_3$ solution. Evipan is chemically and pharmacologically very similar to those barbiturates in common clinical use. A possible explanation is that the observed action of calcium is connected with activation of cholinesterase in the heart. That is, pentothal inhibits cholinesterase (Govier et al. 1953), while calcium has been found to activate it (Mendel et al. 1939, Nachmansohn 1940).

We believe that the results of our studies may be of some value in increasing the safety of intravenous pentothal anaesthesia. Even if the moderate falls in blood pressure which often occur do not endanger normal patients, the circulatory catastrophes described previously may be precipitated by accidental overdosage or the use of more toxic preparations.

As was mentioned in the introduction, blood pressure in hypertensive patients often falls by about 60 mm. Hg during pentothal anaesthesia. Such patients often suffer from latent or manifest ischaemic cardiac disease. In these cases, collateral circulation is of the greatest importance in maintaining

adequate nutrition of the myocardium (Blumgart 1951, Blumgart et al. 1950). It is known that the blood flow through the coronary circuit is dependent primarily on the height of the mean aortic pressure (Gregg 1950, Hochrein 1932, Wiggers 1950). Areas of myocardium supplied by collateral circulation are particularly endangered by a decrease in blood pressure, since a fall of even 20 mm. Hg in pressure gradients may seriously threaten myocardial ischaemia (Prinzmetal et al. 1949, Wiggers 1945). Prolonged hypotension during anaesthesia may thus seriously endanger patients with latent or manifest ischaemic cardiac disease.

Patients suffering from shock, as mentioned above, are also particularly susceptible to the depressant action of sodium pentothal. Such patients may also benefit from the therapeutic reversal of pentothal depression by calcium.

One can also conclude from our studies that the intravenous administration of $CaCl_2$ can increase the safety of i. v. pentothal anaesthesia without causing any change in its duration or depth, particularly in patients with occult or frank myocardial ischaemia and in certain other cases, when the myocardium is already endangered by hypotension as in shock. It should also be possible to make use of the effect of $CaCl_2$ therapeutically in the case of accidental overdosage, or when more toxic preparations are used.

Keszler and Racenberg (personal communication 1954) have tried the intravenous administration of calcium in approximately sixty cases of hypotension occuring in the course of surgery carried out under intravenous barbiturate anaesthesia. With virtually no exception, rapid restoration of the blood pressure to safe levels was obtained.

Summary

1. A weakening of ventricular contraction during intravenous administration of pentothal has been demonstrated with high frequency cardiomyography. A direct depressant action on myocardial muscle by this drug has also been shown following its intracoronary administration.

2. It has been found that falls in blood pressure caused by pentothal are immediately reversible by the intravenous administration of 5—10 ml. of 10% $CaCl_2$.

3. The intravenous administration of $CaCl_2$ affects neither the duration nor the depth of anaesthesia in rabbits.

4. It is emphasized that these findings may be of importance in increasing the safety of intravenous barbiturate anaesthesia:

a) in patients with latent or manifest ischaemic myocardial disease,

b) in patients suffering from shock,
c) in cases of accidental overdosage, or when more toxic preparations are used.

BIBLIOGRAPHY

Adams, R. Ch. (1944): Intravenous Anesthesia, Hoeber, New York.
Beck, C. S. and *Mautz, F. R.* (1937): The Control of the Heart Beat by the Surgeon. Ann. of Surg. 106, 525.
Blumgart, H. L. (1951): Coronary Disease: Clinical-pathological Correlation and Physiology, Bull. of the N. Y. Acad. of Medicine, 27, 693.
Blumgart, H. L., Zoll, P. M., Freedberg, A. S. and *Gilligan, D. R.* (1950): The Experimental Production of Intercoronary Arterial Anastomoses and their Functional Significance, Circulation, 1, 10.
Buhr, G. (1951): Das Verhalten d. physik. Kreislaufgrößen und die Herzdynamik während der Evipan-Na Narkose b. Menschen, Dtsch. Arch. klin. Med. 199, 45.
Dale, W. A. (1952): Cardiac Arrest. Ann. of Surg. 135, 376.
Danielopolu, D. (1922): Les sels de $CaCl_2$ dans l'asystolie. La Presse médicale, 30, 413.
Deusberg, R. and *Schroeder, W.* (1944): Pathophysiologie und Klinik der Kollapszustände, Hirzel, Leipzig, 53 pp.
Froněk, A. and *Píša, Z.* (1954): Vysokofrekvenční kardiomyografie (High Frequency Cardiomyography), Kardiolog. společnost, 24. 9. 1954, in press. Čs. fysiologie.
Frunder, H. (1951): Die Wasserstoffionenkonzentration im Gewebe lebender Tiere, Fischer, Jena.
Girundt, O. (1932): Die Ermittlung der Wirkungsstärke von Schlafmitteln mit Hilfe der Körperstell- und Labyrinthreflexe. I. Mitt.: Die relative Wirkungsstärke von Novonal, Neodorn und Veronal. Arch. F. Exp. Pathol. u. Pharmacol., 164, 118.
Govier, W. M., Freyburger, W. A., Gibbons, A. J. and *Smite, E.* (1953): The Relation of the Choline Cycle to Cardiac Decompensation. Am. Heart J., 45/22.
Gregg, D. (1950): The Coronary Circulation in Health and Disease, Lea and Fabiger, Philadelphia.
Gross, R. E. (1953): The Surgery of Infancy and Childhood, Saunders, Philadelphia, 909 pp.
Hansen, A. T. (1949): Pressure Measurement in the Human Organism, Teknisk Forlag, Copenhagen.
Harris, T. A. B. (1951): The Mode of Action of Anaesthetics, Livingstone, Edinburgh.
Haynal, E. and *Held, R.* (1950): Kreislaufinsuffizienz infolge Barbitursäurevergiftung. Klin. Wschft., 28, 612.
Hochrein, M. (1932): Der Koronarkreislauf, Springer, Berlin.
Jacobi, C. and *Roemer, C.* (1911): Untersuchungen zur Pharmakologie des Veronals. Arch. exp. Path. et Pharm., 66, 241; 66, 261; 66, 296.
Johnston, R. L. (1936): Action of Barbiturates on Heart. J. Pharm., 57, 333.
Johnston, R. L. (1938): Cardiac Depression by Barbituric Acid Derivatives and Relative Antidotal Action of Certain Cardiac Stimulants. J. Pharm. Exp. Therap., 64, 330.
Kay, J. H. and *Blalock, A.* (1951): Use of $CaCl_2$ in Treatment of Cardiac Arrest. Surg., Gynec. and Obstetrics, 93, 97.
Keszler, H. (1954): Personal communication.

Kunzová, H. (1941): Vliv mýdel na činnost srdce (Influence of Soaps on Cardiac Activity), Časopis lékařů českých, 899.

Kunzová, H. (1941): Způsob účinku hypnotik na isolované srdce (The Method of Action of Hypnotics on the Isolated Heart). Časopis lékařů českých, 782.

Magnus, R. (1922): Beiträge zur Pharmakologie der Körperstellung und der Labyrinthreflexe, Acta otolaryngologica, 4, 21.

Magnus, R. (1925): Contributions to the Pharmacology of Posture and of Labyrinth Reflexs. XIX. Comm.: Pyramidon, veramon and veronal with special references to the complicated evolution of stimulant and depressive action upon the central nervous system of mammals. J. Pharm. Exp. Therap., 29, 35.

Mandel, B., Mundell, D. B. and *Strelitzt* (1939): Cholinesterase and Electrolytes. Nature, 144, 479.

Locket, S. and *Angus, J.* (1952): Poisoning by Barbiturates; Success of Conservative Treatment. Lançet 1/12, 580.

Nachmansohn, D. (1940): Action of Ions on Cholinesterase. Nature, 145, 513.

Nikolajev, M. P. (1948): Textbook of Pharmacology, Medgiz, Moscow, 79 pp.

Píša, Z. and *Froněk, A.* (1954): Vliv změn kontrakce myokardu na ekg (The Influence of Changes in Myocardial Contraction upon the Electrocardiograph). In press.

Prinzmetal, M., Corday, E., Bergman, H. C., Schwarz, L. L. and *Spritzler, R. J.* (1949): Studies on the Coronary Circulation. IV. The Effects of Shock on the Heart; its Treatment. Am. Heart J., 37, 560.

Racenberg I. (1954): Personal communication.

Roth, R. (1935): Effects of Barbiturates on the isolated Heart. Arch. Int. Pharmacol. et Pharmacodin., 51, 179.

Rothlin, E. and *Cerletti, A.* (1952): Beitrag zur Frage der Kreislaufwirkung des Calcium. Cardiologia (Basel), 21, 735.

Schoenwald, G. (1940): Action of Veritol on Blood Pressure and Heart Under Various Anesthetics. Lancet 1, 544.

Stephenson, H. E. Jr. (1953): Some Common Denominators in 1200 cases of Cardiac Arrest. Ann. of Surg., 137, 731.

Šrec, F. (1953): Farmakodynamika liekov so stranky experimentalnej a klinickej (The pharmacodynamics of drugs from the experimental and clinical point of view). Slovenská akademie vied, Bratislava, 66 pp.

Tennant, R. (1935): Factors Concerned in the Arrest of Contraction in an Ischemic Myocardial Area. Am. J. Physiol., 113, 677.

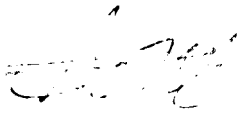
Vokoun, J. Sova, J. and *Šimáně, Č.* (1952): Vysokofrekventní rheoplethysmografie jako metoda ke stanovení rychlostí pulsové vlny (High frequency Impedance Plethysmography as a Method of Determining the Rapidity of the Pulse Wave). Časopis lékařů českých, 91, 947.

Vokoun, J. (1953): Chirurgické léčení chlop. vad srdečních (The Surgical Treatment of Cardiac Valvular Diease). Naše vojsko, Prague.

Wezler, K. and *Thauer, R.* (1942): Die Kreislaufwirkung der gebräuchlichsten tierexperimentellen Narkotica. Arch. exp. Path. u. Pharmacol., 200, 84.

Wiggers, C. J. (1950): Physiology in Health and Disease, Kimpton, London, 772 pp.

Wiggers, C. J. (1945): The Functional Consequences of Coronary Occlusion. Ann. Int. Med., 23, 158.



Chronic Pyelonephritis and Hypertension

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(Read by K. WEBER)

If we are inclined today to consider the kidney in hypertensive disease not as the culprit but as a victim of a disease process starting somewhere else in the body, we still cannot doubt that the diseased kidney is the cause of hypertension in the late stages of chronic glomerulonephritis. Many tacitly assume that the rise of blood pressure in chronic glomerulonephritis is due to an overproduction of hypertensin, although we are no more successful with its demonstration in systemic or renal venous blood here than in hypertensive disease.

The situation seems to be different with chronic pyelonephritis. According to Raaschou this disease is the most prevalent of renal diseases. Our knowledge of this condition is, however, very inadequate; its symptomatology is very poorly worked out and its diagnosis by the usual clinical means—with the exception of cases with a clear-cut history and gross pyuria—is usually uncertain. Opinions about the changes of blood pressure in this condition differ widely. On the one hand it is well known that even serious chronic pyelonephritis may develop without any elevation of the blood pressure. On the other hand the finding of hypertension in subjects with pyelonephritis is attributed by many authors, without hesitation, to a disturbed renal blood supply. Others argue that the incidence of the hypertension in chronic pyelonephritis—especially unilateral disease—is similar to its incidence in the general population; they conclude, therefore, that high blood pressure in chronic pyelonephritis is due to a fortuitous coincidence of chronic pyelonephritis with hypertensive disease. There is yet another extreme view, namely that chronic pyelonephritis or some other abnormality of the urinary passages is the etiology of more than one half of the cases of "essential" hypertension.

It is clear that this great divergence of opinions about blood pressure in chronic pyelonephritis is due in the first place to the difficulty in recognizing this disease. Raaschou has contributed much to an improvement in its diagnosis by a thorough clearance investigation. However, the nature of the method makes its application in everyday clinical practice unsuitable.

We happened to investigate renal function six years ago in a subject who died with the clinical picture of malignant hypertension and in whom the autopsy revealed chronic pyelonephritis. The functional findings, which before the biopsy were incomprehensible to us, led us to the belief that chronic pyelonephritis differs from other renal diseases by its renal functional pattern. This may be easily established by simple laboratory means which are within the reach of the majority of even small

TABLE I *Symptoms of pyelonephritis.*

Clinical picture	Number	Urinary deposit			Renal functions					Urography					Bacteriol.	
		Norm.	Pyuria	Haematuria	Norm.	Typical dissoc.	Fixation spec. w. below 1012	Resorpt. below 99 %	Not invest.	Norm.	Hydronephrosis	Stone	Hypo- or afunction or other abnorm.	Not invest.	Negat.	Posit.
Cystopyelitis	66	1	55	10	11	52	6	8	3	13	22	9	11	15	6	44
Nephrolithiasis . . .	19	—	9	10	1	18	—	9	- -	1	10	10	—	2	—	9
Unspecific symptoms (pyelonephritis certain or very likely) .	24	—	20	4	1	22	7	18	1	2	10	2	6	6	3	11
Unspecific symptoms. Pyelonephritis uncertain	16	—	13	3	1	14	2	8	1	6	—	—	4	6	1	10
Diagnosis unconfirmed on autopsy	2	- -	2	—	—	2	2	2	—				1	1	1	1
Total	127	1	99	27	14	108	17	45	5	22	42	21	22	30	11	75

Note: Bacteriological investigation was carried out only in one part of the cases.

hospital laboratories. This specific functional pattern may thus be used to establish the diagnosis of chronic pyelonephritis. It consists of the following changes: (1) A disproportionate prevalence of leucocytes over erythrocytes in the quantitative Addis count (the hyperaemic mucosa of the urinary passages might, of course, bleed occasionally, in which case this typical change of the deposit is lost—haematuria thus does not exclude the presence of chronic pyelonephritis). For the discovery of this change an ordinary examination of the urinary deposit is inadequate. (2) The function of the distal tubule is damaged to a higher extent than the function of the glomeruli; we find, therefore, a marked hyposthenuria or isosthenuria along with a relatively satisfactory glomerular filtration (clearance of "endogenous" creatinine). With unilateral disease it is necessary to realise that the isosthenuric urine of the diseased kidney is mixing with the normally concentrated urine of the healthy kidney and that the final specific gravity depends on the ratio of the urines of the two kidneys. (3) The degree of the tubular reabsorption of water is depressed frequently below the usual daily average of 99.0–99.2 % of the filtered amount. In more advanced forms of the disease the facultative reabsorption of water in the distal tubule stops altogether and the rate of tubular reabsorption falls towards 85–90 %. The resulting polyuria is much more striking than the polyuria of chronic glomerulonephritis. (4) The specific gravity of urine from the diseased kidney frequently becomes fixed, contrary to glomerulonephritis, at values below 1012.

Intravenous pyelography may help in the recognition of unilateral disease and,

along with retrograde pyelography, it may yield information about the distortion in the shape of the calyces, renal pelvis or ureters. However, it may also be normal and, in general, it is impossible to base the diagnosis of chronic pyelonephritis on an abnormal shape of the urinary passages.

With these new possibilities in the clinical diagnosis the question of hypertension in connection with chronic pyelonephritis was reviewed. It was first necessary to

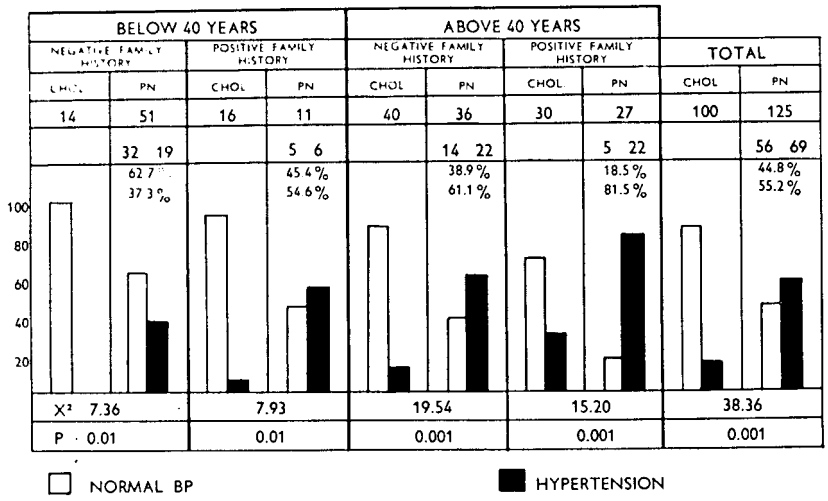

Fig. 1.

establish that the described functional pattern is really specific for chronic pyelonephritis. In the last 6 years we made this diagnosis in 127 patients (Table I). Typical changes in the urinary deposit were found in 99, whereas in 27 erythrocytes were prevalent and only in 1 patient with a grave renal functional disturbance was the Addis count normal. 66 of these subjects (i.e. 52 %) suffered from distinct cytopyelitic symptoms (dysuria, frequency of micturition, pain in the loins, occasional temperature rise). 52 of these had the above-mentioned functional changes while 3 were not sufficiently investigated. Of the 50 patients with renal calculi which we have examined since 1948, 19 had renal functional changes or signs of inflammation in the urinary passages. 18 of them had the above-mentioned functional pattern. 42 patients (33 %) were examined for some other symptoms which did not point directly to pyelonephritis: half of them for proteinuria which was found by accident, others for signs of cardiac or renal failure, back pain, haematuria, head-ache, high blood pressure, anorexia etc. In 36 of them the described dissociation between the glomerular and tubular function was found, 1 was not fully investigated and in 2 function was normal. Objection may be raised to the actual proof that these last 42 subjects really suffered from chronic pyelonephritis. This question may be answered on the basis of urological investigation, urography, renal biopsy or autopsy, all in the

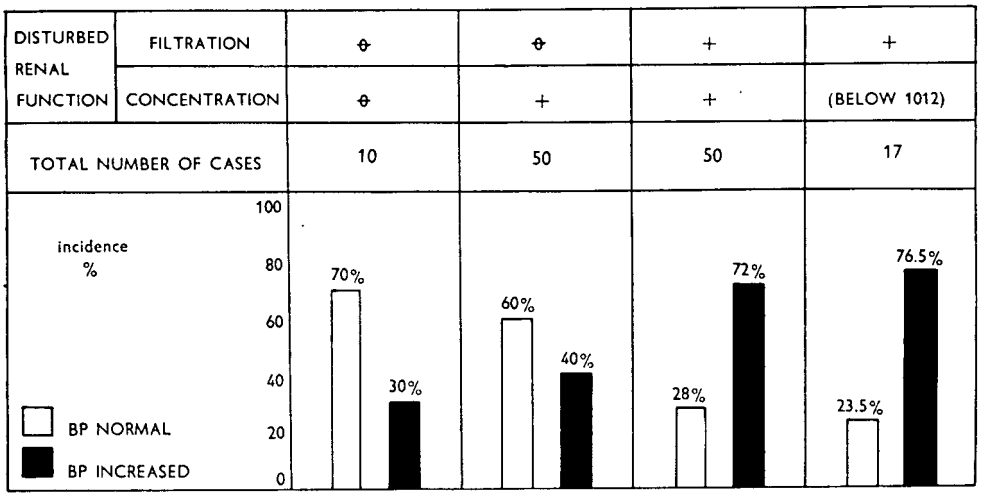

Fig. 2.

affirmative in 22. In a further 2 the diagnosis was highly probable. Of the remaining 18 subjects it is not possible to exclude the diagnosis in 16: 13 of them had microscopic pyuria, and in 10 of the 11 examined bacteriologically, the urine was infected. Only in 2 females who died was it impossible to verify the diagnosis by necropsy, the post-mortem showing only serious nephrosclerosis without signs of pyelonephritis in one, and thrombosis of the renal artery with renal contraction in the other.

It may thus be concluded that, so far, only 2 of the 108 persons in whom this functional pattern was found had no chronic pyelonephritis. In 92 the diagnosis may be considered as firmly established. 13 of the remaining 14 had a microscopic pyuria and in 10 the urine was infected. We may, therefore, u e this functional pattern to establish—with a high degree of probability—the diagnosis of chronic pyelonephritis.

Let us consider next the behaviour of blood pressure in cases of chronic pyelonephritis diagnosed in this way. The results are summarized in Fig. 1. where the incidence of high blood pressure in our patients with chronic pyelonephritis is compared with the incidence of hypertension in 100 subjects with chronic cholecystitis. Because of the previously mentioned objection of some authors that high blood pressure in chronic pyelonephritis merely means a chance coincidence of pyelonephritis and hypertensive disease, we have divided our patients into an age group below 40 years when hypertensive disease is relatively rare, and above 40 when its incidence rises markedly. A further subdivision into subjects with and without family history of hypertension was necessitated by the fact that the incidence of hypertensive disease is much higher in the first group. It may be seen at first sight that in all subgroups the incidence of hypertension in our subjects with chronic pyelonephritis is much

TABLE II *Relation of hypertension to a unilateral disease.*

Clinical picture	Unilateral disease		Bilateral disease	
	Blood pressure		Blood pressure	
	Normal	Elevated	Normal	Elevated
Cystopyelitis	13	14	10	11
Lithiasis	8	5	1	4
Other symptoms . .	7	7	7	11
Total	28	26	18	26

above that in chronic cholecystitis. As might be expected, hypertension is more frequent in the older age group, having been encoutered in more than 2,3 of the patients. Its incidence is especially impressive in the sub-group over 40 with a positive family history, where 81.5 % of all subjects had a high blood pressure. However, in the younger age group the incidence of 25 out of 62 patients, i.e. 40.3 %, was also far above the incidence of high blood pressure in the general population of that age. The incidence of hypertension in subjects with a negative family history (37.3 %) was not much below the average incidence for the whole younger age group. The overall incidence of hypertension in all our subjects with chronic pyelonephritis was 55.2 %, differing strikingly from the 15 % incidence in the whole group of subjects with chronic cholecystitis.

It follows from Fig. 2 that the incidence of hypertension increases with the degree of renal damage but it is high also in subjects whose rate of glomerular filtration is within the normal range.

Table II gives at least a partial answer to the question as to what extent unilateral renal disease might be the cause of a raised blood pressure. It may be seen that, based on radiological and urological findings, we were able to express our opinion whether one or both kidneys are affected in 98 subjects. The disease was predominantly unilateral in 54: 26 (i.e. 48.2 %) of these had hypertension. The incidence of hypertension in the bilateral disease is somewhat higher (59 %) but the difference is not great. The result also speaks in favour of a narrow relationship between a unilateral kidney disease and hypertension.

This follows, moreover, from the numerous reports of cured hypertensions following the removal of pyelonephritic kidney. Such cases are suffciently well known today so that I may abstain from presenting a further striking example of such a cured malignant hypertension which we have had under observation for the past 2 years.

This case brings out, however, a further important point about hypertension in chronic pyelonephritis, namely, that it may take on a malignant course. This occurred in 11 out of our 69 pyelonephritics with hypertension, i.e. in 15,9 %. This incidence is

TABLE III *Chronic pyelonephritis with malignant hypertension.*

Name	Sex	Age	Positive family history of hypertension	History of cysto pyelitis or lithiasis	Urinary deposit		Glomerular filtration rate	Isosthenuria	Spec. grav. below 1012	Autopsy or biopsy
					Leucocytes	Erythrocytes				
B. V.	M.	35	–	–	+		10	+		?
B.-A.	F.	58	–	–	+		10	+	+	P.-N.
G. E.	F.	26	–	–	+		7.8	+	+	?
K. S.	F.	54	+	–	+		14.2	+	+	Nephroscler.
V. J.	M.	40	+	–		±	25	+	+	P.-N.
V. O.	F.	46	+	–	+		60.3	+	+	Nephroscler.?
Z. V.	F.	38	–	–	+		4.38	+	+	P.-N.
M. K.	F.	25	–	–	+		92	+		P.-N.
S. L.	M.	43	–	–		±	41	+	+	P.-N.
M. H.	F.	52	+		+		9.5	+	+	
A. P.	M.	42	–			+	1.4	+	+	P.-N.

similar to the incidence of the malignant course of hypertension in hypertensive disease. The data of all of these 10 subjects are shown in Table III. It may be seen that they all had a similar functional pattern, namely, isosthenuria which in 9 of them was fixed below 1012. On the other hand the rate of glomerular filtration was below 25 ml/1 min. only in 7. In 8 leucocytes were prevalent in the urinary deposit. In 2, whose diagnosis was confirmed by autopsy, the urinary deposit was quite insignificant. In 6 the diagnosis of pyelonephritis was confirmed by autopsy or biopsy, in 1 an autopsy was not performed. In 2 females whose clinical and functional picture did not differ in the least from the findings in other patients, only signs of a grave malignant nephrosclerosis or renal artery thrombosis were found on autopsy. It is interesting to note that there was nothing in the past history of any of these patients that would suggest a disease affecting the renal pelvis or the urinary passages.

The relation between this very serious renal disease and hypertension is shown in Table IV. It may be seen that this functional pattern was found in 20 subjects (i.e. 15.7 %) of which 16 (i.e. 80 %) had hypertension. In one half of these the hypertension was malignant. A positive family history of hypertension could be found only in 6 of these patients.

We may now draw the following conclusions:

1. The functional changes which we have described are highly suggestive of chronic pyelonephritis.

2. The incidence of hypertension in subjects with chronic pyelonephritis is far

TABLE IV *Pyelonephritis with fixation of the specific gravity of urine below 1012.*
(Out of 127 cases of pyelonephritis.)

Number	Family history of hypertension	Hypertension	Malignant hypertension
20	6	16 (80 %)	8

above the incidence in subjects suffering from other chronic diseases and significantly exceeds the incidence of hypertension in the general population.

3. Although the incidence of hypertension is higher in subjects whose kidneys are gravely damaged by the disease process, it is also strikingly high in subjects whose renal function is little altered.

4. The frequency of the malignant course of hypertension in subjects with pyelonephritis and high blood pressure is similar to that of subjects with hypertensive disease. Malignant hypertension has been found especially in cases with a very severe renal lesion.

5. Although the incidence of hypertension is higher in subjects with a family history of hypertension, especially if they are over 40 years of age, it is also very frequent in subjects below 40 with a negative family history. This speaks against a chance coincidence of chronic pyelonephritis and hypertensive disease and corroborates the view that chronic pyelonephritis is the cause of the elevation of the blood pressure. This, of course, does not necessarily mean that a renal humoral mechanism is reponsible for the rise in blood pressure. Hypertension in subjects with a perfectly normal glomerular filtration, does not favour this view although it does not disprove it. On the other hand the 80 % incidence of hypertension in pyelonephritics over 40 with a positive family history, brings out the question of whether pyelonephritis has some causal connection with the origin of true hypertensive disease. This has already been suggested by Braasch (122). A clinical symptomatology indistinguishable from that of the early stages of hypertensive disease speaks in favour of this idea. It is further corroborated by the findings of Fencl and Hejl that the dynamic cold pressor test gives a significantly higher incidence of "hyperreactors" among normotensive subjects with chronic pyelonephritis than among normotensive subjects without any renal disease. It is a common experience with the new antihypertensive drugs that chronic pyelonephritis with hypertension yields to an adrenergic blocking agent, in the same way as the raised blood pressure of early hypertensive disease, but unlike the hypertension produced by renal pressor substances.

It is a fact there is a multitude of sensory nerve endings on the renal vessels both in their extrarenal and in their intrarenal course. Thus there is a possibility for a

disturbance of the central nervous regulating mechanisms by a host of abnormal stimuli from the diseased kidneys. There is, therefore, a possibility for a disturbance of the central nervous regulating mechanisms of blood pressure, which we think is the basis of the development of hypertensive disease.